Synthetic Studies toward Hennoxazole A. Use of a Selective Bisoxazole Alkylation as the Key Fragment Coupling

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SYNTHETIC STUDIES TOWARD HENNOXAZOLE A. USE OF A SELECTIVE BISOXAZOLE ALKYLATION AS THE KEY FRAGMENT COUPLING

Thomas E. Smith* and Emily P. Balskus

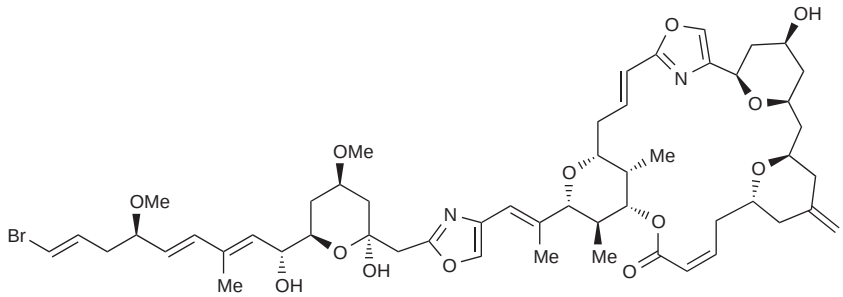
Department of Chemistry, Williams College, 47 Lab Campus Drive, Williamstown, MA 01267, USA. tsmith@williams.edu

Abstract – A model system for side chain fragment coupling to the core of hennoxazole A is investigated. Lateral metallation of a C_{13}-TBS-protected bisoxazole, using lithium diethylamide, allows for selective and efficient alkylation at C_{15}.

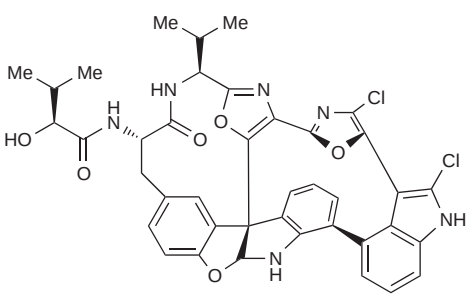
INTRODUCTION

Marine natural products containing the oxazole nucleus have drawn considerable attention recently (Figure 1). Synthetic studies of complex molecules containing isolated 2,4-disubstituted oxazole units such as the phorboxazoles,[1] bisoxazoles such as the hennoxazoles[2] and diazonamides,[3] and trisoxazoles such as the ulapualides,[4] have contributed methods for the assembly of these systems and have resulted in several total syntheses. The development of relatively mild oxazole-forming reaction sequences[5] has

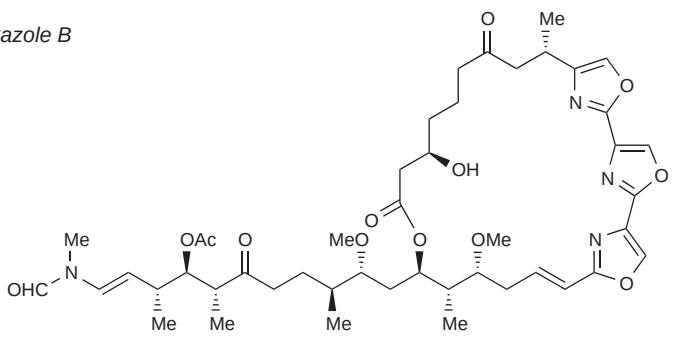
Figure 1. Oxazole-Containing Marine Natural Products



Phorboxazole B



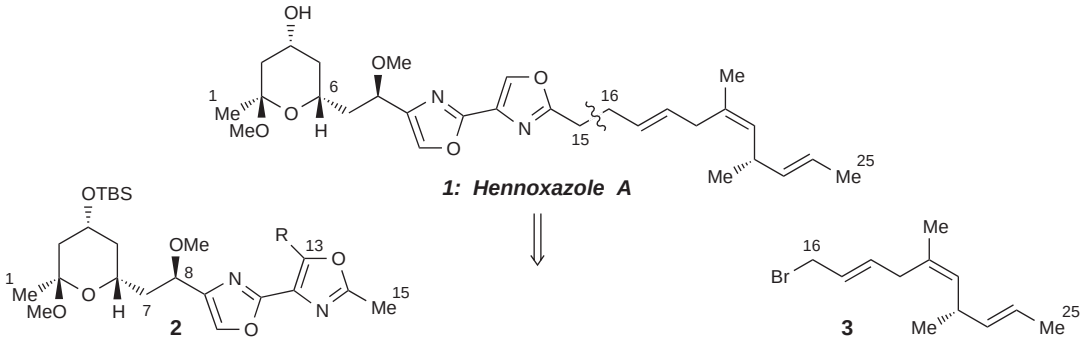
Diazonamide A



Ulapualide A

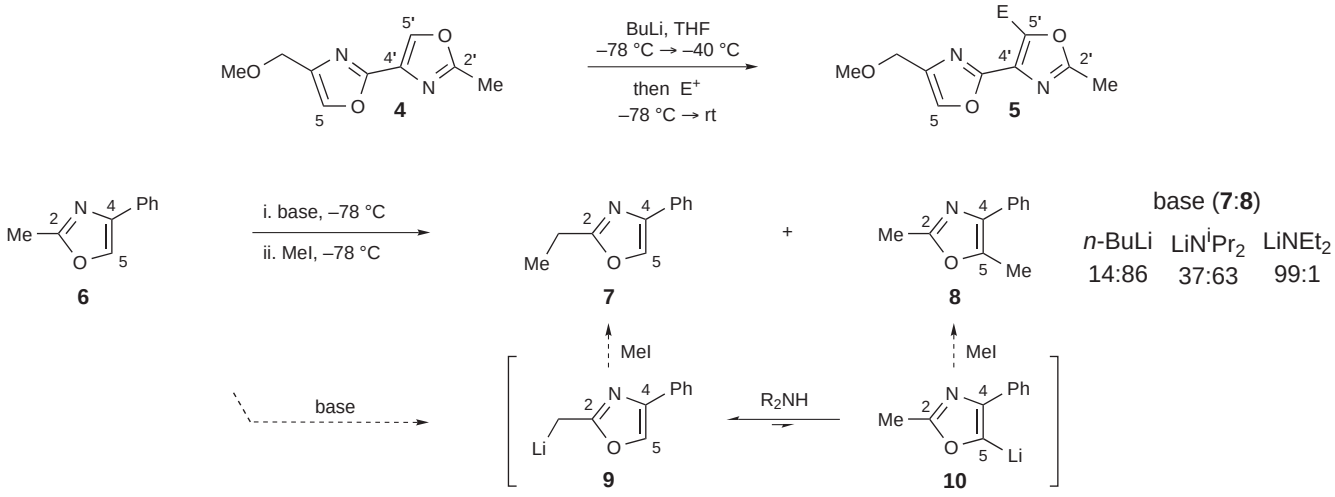
made the late-stage creation of these ring systems a common strategy—with cleavage of an oxazole ring frequently serving as the key disconnection back to major coupling fragments.[6] Approaches involving end game functionalization of *intact* oxazole rings, however, provide the opportunity to use relatively simple oxazoles as starting materials and then efficiently carry these, practically inert,[7] heterocycles through a variety of synthetic transformations.[8] In consideration of these issues, our synthesis plan for hennoxazole A (**1**, Scheme 1) involves late-stage construction of the C_{15}–C_{16} bond by metallation of a relatively elaborate bisoxazole (**2**) at the C_{15}-methyl position, followed alkylation with an allylic halide C_{16}–C_{25} side chain fragment (**3**).[9]

Scheme 1. Retrosynthetic Analysis for Hennoxazole A



Synthetically useful lateral metallations of some 2-methyl-oxazole and -thiazole systems have been reported.[10] If these rings are unsubstituted at C_5, however, competitive deprotonation of the C_5-ring hydrogen is frequently observed (Scheme 2).[11] In fact, Williams has shown that bisoxazole **4** is lithiated with *n*-BuLi exclusively at the $C_{5'}$-ring position,[12] suggesting that alkylation of **2** at C_{15} may be problematic if R = H. Despite this result, previous work confronting a similar problem in the synthesis of phorboxazole, demonstrated that the regioselectivity of some oxazole deprotonations can be altered by the use of lithium diethylamide.[13] As elaborated in the preceding communication,[14] deprotonation of

Scheme 2. Oxazole and Bisoxazole Alkylations



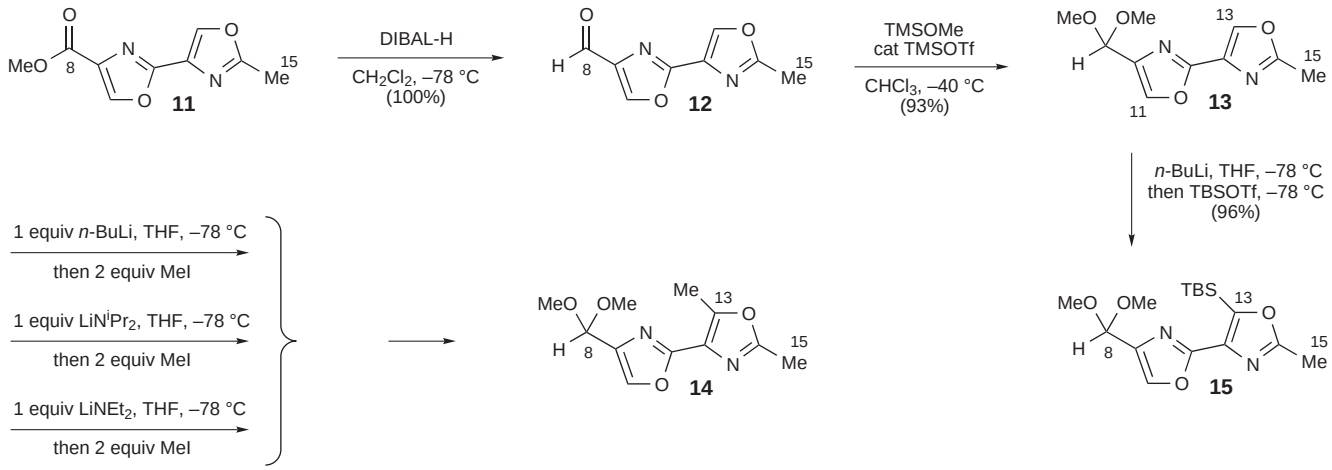
2-methyl-4-phenyloxazole (**6**) using *n*-BuLi at –78 °C followed by alkylation with methyl iodide gives a 14:86 ratio of products (**7**:**8**) favoring ring methylation, while the use of $LiNEt_2$ leads to alkylation solely at the C_2-methyl site. This reversal of regioselectivity is thought to arise from the ability of diethylamine to mediate the low-temperature equilibration of a kinetic mixture of otherwise noninterconverting lithiated intermediates (**9** and **10**).[15]

Herein we report our results on a model fragment coupling for hennoxazole A using lithium diethylamide.

RESULTS AND DISCUSSION

To test the viability of our key side chain coupling strategy, we first prepared bisoxazole (**13**) as a model substrate (Scheme 3). Bisoxazole ester (**11**)[16] was reduced with DIBAL-H in CH_2Cl_2 at low temperature to give aldehyde (**12**)[17] in quantitative yield. Dimethyl acetal (**13**) was then generated under Noyori conditions[18] in 93% yield. In results consistent with Williams' studies of **4**,[12] treatment of bisoxazole (**13**) with *n*-BuLi led to deprotonation exclusively at the C_{13} ring position (hennoxazole numbering), with no deprotonation occurring at the C_{15}-methyl group. For this substrate, replacing the base with LDA or $LiNEt_2$ did not alter the regioselectivity, suggesting that deprotonation at C_{13} is both kinetically and thermodynamically favored.[19] Attempts to alkylate the dianion of **13** were not fruitful. To circumvent this dilemma, we chose to block C_{13} with a silyl protecting group.[20] Although TMS and TES groups were found to be too labile under these metallation conditions, the TBS group proved to be suitable. Treatment of **13** with *n*-BuLi followed by addition of TBSOTf led to C_{13}-protected bisoxazole (**15**) in 96% yield.

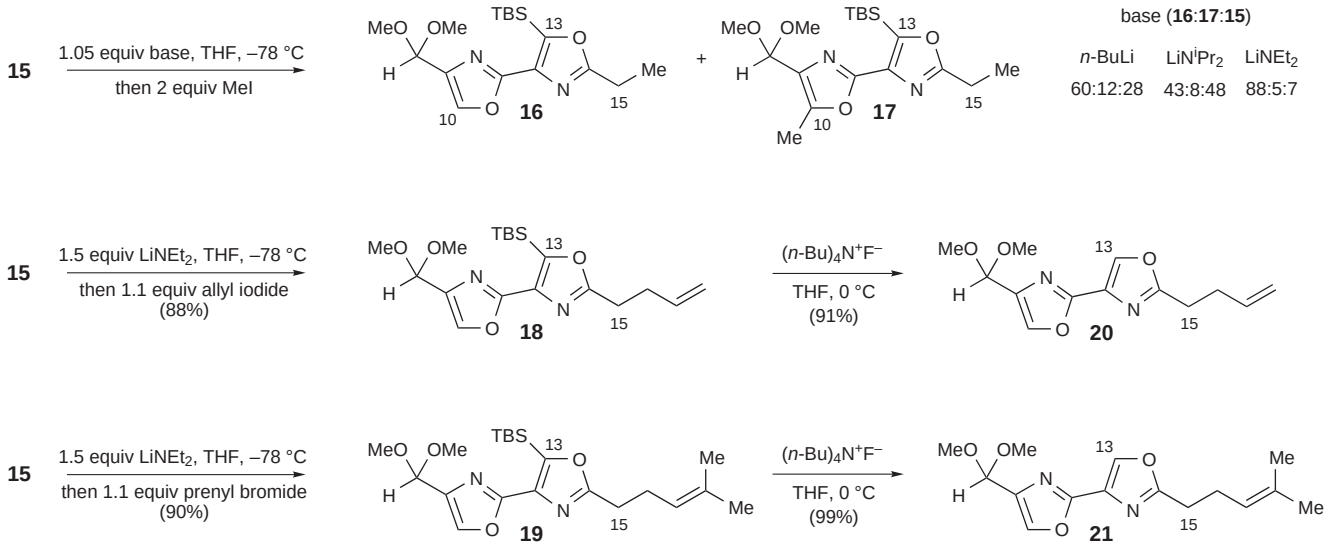
Scheme 3. Preparation of a Hennoxazole Model System



To model our key coupling step, we treated protected bisoxazole (**15**) with several different strong bases and quenched with MeI (Scheme 4). Gratifyingly, alkylation occurred at the desired C_{15} site, with $LiNEt_2$ providing the best results. It is interesting to note that *n*-BuLi and LDA both gave poor conversion and small amounts of product **17**—methylated at *both* at the C_{15}-methyl and C_{10}-ring positions—at the

expense of starting material conversion.[21] No significant monomethylation at C_{10} was observed. We speculate that this result could potentially arise from rate differences of the C_{10}- and C_{15}-anions with respect to alkylation and intermolecular proton exchange. Chelation of lithium between C_{10} and an oxygen atom of the C_8-dimethyl acetal could decrease the reactivity at this center and lead to the observed product mixtures. To better mimic the reactivity of the actual side chain fragment (**3**), we also alkylated **15** with allyl iodide and prenyl bromide, both of which gave excellent results with $LiNEt_2$.[22] Finally, treatment of alkylated products (**18**) and (**19**) with TBAF demonstrated that the oxazole could be cleanly deprotected under mild conditions.[23]

Scheme 4. Hennoxazole Side Chain Alkylation Model Studies



CONCLUSION

Selective alkylation of a C_8–C_{15} model for the bisoxazole portion of hennoxazole A is possible using lithium diethylamide when the C_{13}-position is blocked. Thus, modification of our initial retrosynthetic analysis (Scheme 1) to include a silyl protecting group at C_{13} (R = TBS) should provide a successful fragment coupling approach to hennoxazole A. Further reports on this synthesis will be forthcoming.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. (a) C. J. Forsyth, F. Ahmed, R. D. Cink, and C. S. Lee, *J. Am. Chem. Soc*., 1998, **120**, 5597. (b) D. A. Evans, D. M. Fitch, T. E. Smith, and V. J. Cee, *J. Am. Chem. Soc*., 2000, **122**, 10033. (c) A. B. Smith, III, K. P. Minbiole, P. R. Verhoest, and M. Schelhaas, *J. Am. Chem. Soc*., 2001, **123**, 10942.
2. (a) P. Wipf and S. Lim, *J. Am. Chem. Soc*., 1995, **117**, 558. (b) D. R. Williams, D. A. Brooks, and M. A. Berliner, *J. Am. Chem. Soc*., 1999, **121**, 4924. (c) F. Yokokawa, T. Asano, and T. Shioiri,

Tetrahedron, 2001, **57**, 6311.

3. J. Li, S. Jeong, L. Esser, and P. G. Harran, *Angew. Chem. Int. Ed.*, 2001, **40**, 4765 and references cited therein.
4. S. K. Chattopadhyay and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2429 and references cited therein.
5 (a) A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, and D. R. Williams, *Org. Lett.*, 2000, **2**, 1165. For a review of classical methods of oxazole synthesis see: (b) I. J. Turchi, 'Oxazoles' in 'Heterocyclic Compounds,' Vol. 45, ed. by I. J. Turchi, Wiley, New York, 1986. (c) F. W. Hartner, 'Oxazoles,' in 'Comprehensive Heterocyclic Chemistry II,' Vol. 6, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford, 1996, pp. 262–318 and references cited therein.
6. See references 1a, 2a, and 2c. See also: (a) J. C. Muir, G. Pattenden, and R. M. Thomas, *Synthesis*, 1998, 613. (b) S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon, and D. Waite, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2415.
7. For a review of the uses of oxazoles as protected carboxylate equivalents see: H. H. Wasserman, K. E. McCarthy, and K. S. Prowse, *Chem. Rev.*, 1986, **86**, 845. See also: references 5b and 5c.
8. See references 1b, 1c, 2b, and 4. See also: (a) P. Liu and J. Panek, *Tetrahedron Lett.*, 1998, **39**, 6143 and 6147. (b) C. M. Shafer and T. F. Molinski, *J. Org. Chem.*, 1998, **63**, 551. (c) J. V. Schaus and J. S. Panek, *Org. Lett.*, 2000, **2**, 469. (d) A. B. Smith, III, K. P. Minbiole, and S. Freeze, *Synlett*, 2001, 1739.
9. For total syntheses of hennoxazole A, see reference 2. For synthetic studies, see: (a) A. G. M. Barrett and J. T. Kohrt, *Synlett*, 1995, 415 (b) Z. Cheng, Y. Hamada, and T. Shioiri, *Synlett*, 1997, 109. (c) T. Shioiri, N. McFarlane, and Y. Hamada, *Heterocycles*, 1998, **47**, 73. (d) A. Vakalopoulos and H. M. R. Hoffmann, *Org. Lett.*, 2001, **3**, 177.
10. (a) B. Lipshutz and R. Hungate, *J. Org. Chem.* 1981, **46**, 1410. (b) S. E. Whitney and B. Rickborn, *J. Org. Chem.*, 1991, **56**, 3058. (c) E. Vedejs and M. A. Zajac, *Org. Lett.*, 2001, **3**, 2451. (d) D. A. Entwistle, S. I. Jordan, J. Montgomery, and G. Pattenden, *Synthesis*, 1998, 603. (e) D. Garey, M. Ramirez, S. Gonzales, A. Wertsching, S. Tith, K. Keefe, and M. R. Pena, *J. Org. Chem.*, 1996, **61**, 4853. (f) J. H. Bowie, P. F. Donaghue, H. J. Rodda, and D. H. Williams, *Org. Mass Spectrom.*, 1968, **1**, 13. See also reference 7.
11. (a) G. Knaus and A. I. Meyers, *J. Org. Chem.*, 1974, **39**, 1192. (b) A. I. Meyers and J. P. Lawson, *Tetrahedron Lett.*, 1981, **22**, 3163. (c) A. I. Meyers and S. Hellring, *J. Org. Chem.*, 1982, **47**, 2999. (d) A. I. Meyers, J. P. Lawson, D. G. Walker, and R. J. Linderman, *J. Org. Chem.*, 1986, **51**, 5111. (e) H. Hamana and T. Sugasawa, *Chem. Lett.*, 1983, 333. For a review of oxazole metallation see: (f) B. Idon, *Heterocycles*, 1994, **37**, 1321.
12. D. Williams, D. Brooks, and K. Meyer, *Tetrahedron Lett.*, 1998, **39**, 8023.
13. D. A. Evans, V. J. Cee, T. E. Smith, and K J. Santiago, *Org. Lett.*, 1999, **1**, 87.
14. T. E. Smith, M. S. Mourad, and A. J. Velander, *Heterocycles*, 2002, **57**, xxxx.
15. The carbanion of **9** may be delocalized into the C=N π system.
16. Known ester (**11**) was prepared in 5 steps following literature procedures. See reference 6b. See

also: D. R. Williams, P. D. Lowder, Y.-G. Gu, and D. A. Brooks, *Tetrahedron Lett.*, 1997, **38**, 331.

17. Aldehyde (**12**) has been reported, but no preparation conditions are given: D. R. Williams, D. A. Brooks, J. L. Moore, and A. O. Stewart, *Tetrahedron Lett.*, 1996, **37**, 983. See reference 23 for spectral data.
18. T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357. See also reference 8a.
19. Williams carried out semiempirical calculations also suggesting that the ring-lithiated intermediate was thermodynamically favored due to chelation with the adjacent oxazole nitrogen (reference 12).
20. Silylation at C_5 was one approach to solving "the oxazole problem" in virginiamycin (a) R. Wood and B. Ganem, *Tetrahedron Lett.*, 1983, **24**, 4391. (b) E. Fujita , *Heterocycles*, 1984, **21**, 41.
21. Product identities and ratios were determined using a combination of ^{1}HNMR and GCMS analysis. All isolated yields are following silica gel chromatography. Spectral data for **12**–**15** and **19**–**21** are given in reference 23.
22. Representative Bisoxazole Alkylation Procedure using $LiNEt_2$: To a solution of diethylamine (22 μL, 0.213 mmol) in THF (1 mL) at –78 °C under Ar was added *n*-butyllithium (133 μL of a 1.5 *M* hexane solution, 0.199 mmol) dropwise. After stirring at –78 °C for 5 min, warming to 0 °C for 10 min, and re-cooling to –78 °C, this solution was added via canula to a solution of bisoxazole (**15**) (48.0 mg, 0.142 mmol) in THF (1 mL). The resulting bright red solution was stirred at –78 °C for 30 min. Allyl iodide (14.3 μL, 0.156 mmol) was added dropwise and the color faded to a light orange. After 15 min, the reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and warmed to rt. The resulting mixture was partitioned between CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the combined organics were dried over a 1:1 mixture of K_2CO_3 and Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel deactivated with 2.5% Et_3N) eluting with 1:4 Et_2O:hexanes to afford the allylated product (**18**, 47.0 mg, 88%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, *J* = 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.3, 6.5 Hz, 1H), 5.45 (d, *J* = 0.6 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.6 Hz, 1H) 4.99 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.36 (s, 6H), 2.94 (t, *J* = 7.9 Hz, 2H), 2.55 (dt, *J* = 7.1, 7.8 Hz, 2H), 0.93 (s, 9H), 0.376 (s, 6H) ppm.; ^{13}C NMR ($CDCl_3$) δ 168.1, 156.8, 155.0, 139.8, 139.1, 136.7, 136.5, 116.1, 98.8, 53.0, 31.2, 27.7, 26.7, 17.8, –5.7 ppm.; IR (neat) 1062, 1103, 1193, 1251, 1391, 1470, 1580, 1612, 2858, 2931 cm^{-1}; Anal. Calcd for $C_{19}H_{30}N_2O_4Si$: C, 60.29; H, 7.99; N, 7.40. Found: C, 60.56; H, 8.02; N, 7.37.
23. Spectral data for other new compounds are as follows:

12: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 10.0 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 2.57 (s, 3H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 184.3, 163.3, 156.6, 143.7, 141.7, 139.6, 129.7, 14.0 ppm.; IR (neat) 3124, 1686, 1295, 1206 cm^{-1}; Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.08; H, 3.45; N,15.70.

13: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H), 7.64 (s, 1H), 5.38 (s, 1H), 3.30 (s, 6H), 2.45 (s, 3H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.8, 155.7, 139.7, 138.5, 137.0, 130.6, 98.6, 53.1, 14.0

ppm.; IR (neat) 3119, 1636, 1530, 1305, 1106, 1058, 984 cm^{-1}; Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.68; H, 5.41; N, 12.41.

14: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 0.8 Hz, 1H), 5.43 (s, *J* = 0.8 Hz, 1H), 3.35 (s, 6H), 2.60 (s, 3H), 2.43 (s, 3H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 160.3, 156.7, 149.9, 139.5, 136.4, 125.2, 98.7, 53.0, 13.8, 11.7 ppm.; IR (neat) 2937, 1593, 1197, 1097, 1055, 980 cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.57; H, 5.97; N, 11.66.

15: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, *J* = 0.9 Hz), 5.45 (d, 1H, *J* = 0.9 Hz), 3.37 (s, 6H), 2.53 (s, 3H), 0.94 (s, 9H), 0.38 (s, 6H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 165.3, 156.8, 155.0, 139.9, 139.2, 136.7, 98.8, 53.0, 26.7, 17.8, 14.0, –5.7 ppm.; IR (neat) 2929, 1611, 1114, 1101, 1061 cm^{-1}; Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.28. Found: C, 56.98; H, 7.67; N, 8.29.

19: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, *J* = 0.9 Hz, 1H), 5.45 (d, *J* = 0.9 Hz, 1H), 5.13 (t, *J* = 7.1 Hz, 1H), 3.36 (s, 3H), 2.85 (t, *J* = 7.3 Hz, 2H), 2.4 (dt, *J* = 7.4, 7.4 Hz, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 0.93 (s, 9H), 0.37 (s, 6H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 168.5, 156.9, 154.8, 139.8, 139.1, 136.7, 133.6, 122.4, 98.8, 52.9, 28.5, 26.6, 25.9, 25.8, 17.82, 17.79, –5.7 ppm.; IR (neat) 2954, 2930, 1469, 1251, 1104, 1062, 843, 124 cm^{-1}; Anal. Calcd for $C_{21}H_{34}N_2O_4Si$: C, 62.03; H, 8.43; N, 6.89. Found: C, 62.17; H, 8.56; N, 6.94.

20: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.17 (s, 1H), 7.71 (d, *J* = 1.0 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.3, 6.5 Hz, 1H), 5.47 (d, *J* = 1.0, 1H), 5.08 (ddt, *J* = 17.1, 3.2, 1.6 Hz, 1H), 5.02 (ddt, *J* = 10.2, 2.8, 1.2 Hz, 1H), 3.38 (s, 3H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.58 (dt, *J* = 6.6, 6.6 Hz, 2H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 165.6, 155.8, 139.8, 138.5, 137.1, 136.3, 130.5, 116.4, 98.6, 53.1, 30.1, 27.8 ppm.; IR (neat) 2939, 1103, 1059, 984, 916 cm^{-1}; Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.94; H, 6.16; N, 10.46.

21: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.16 (s 1H), 7.70 (d, *J* = 0.9 Hz, 1H), 5.46 (d, *J* = 0.8 Hz, 1H), 5.11 (t, *J* = 7.1 Hz, 1H), 3.74 (s, 6H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.48 (dt, *J* = 7.4, 6.8 Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H) ppm.; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 166.0, 155.8, 139.7, 138.4, 137.0, 133.9, 130.4, 122.0, 98.6, 53.0, 28.5, 25.8, 25.7, 17.8 ppm.; IR (neat) 2933, 1103, 1059, 984 cm^{-1}; Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.38; H, 7.06; N, 9.36.